REMARKS

This amendment after a final rejection should be entered pursuant to 37 CFR 1.116(c). The amendment to claim 55 were not earlier presented because the Fecondini prior art reference was newly applied in the final rejection and the amendments further distinguish the claimed invention from the combination of Fecondini and Shittigar.

The rejection of claims 55 to 71 as being obvious over US Patent 5,211,850 (Shettigar) in view of US Patent 4,861,485 (Fecondini) is traversed.

The claims of this application are directed to ultrafiltration by a small sized filter having a filter membrane surface area of less than 0.2 m^2 that block solutes in blood of greater than 60,000 Daltons in size. Prior ultrafiltration systems required much larger membrane surface areas to handle high volume blood flow rates that were previously believed necessary to perform therapeutic blood treatments. *See* Specification, pages 12-15 and 29-30.

Applicants recognized that ultrafiltration can be effectively preformed by small filters operating at relatively low blood flows. The applied prior art does not teach that ultrafiltration may be performed with small filters and low blood flow rates. The claimed invention was not obvious at least because the prior art does not disclose ultrafiltration being effectively preformed with small filters. *In re Zurko*, 42 USPQ2d 1476 (Fed. Cir. 1997) ("to say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art.").

The blood purification system disclosed in Shettigar is distinct from ultrafiltration. Shettigar describes a system and method of achieving both convective and diffusive transport of plasma across a membrane accompanied by the selective removal of plasma components using sorbents followed by reinfusion of the purified plasma in a blood circulation system is achieved by pumping blood through a filter comprising a bundle of "U" shaped hollow fibers immersed in a closed plasma chamber containing sorbents in an electrolyte solution. Shettigar combines a plasmapheresis filter and an absorbent technology to remove specific components from the blood in a U shaped filter media configuration avoiding the use of a second pump. Shettigar, col. 1, lns. 28-30 ("Ultrafiltration . . . techniques do not utilize a purification medium."). The blood purifier disclosed in Shettigar has filter membranes that purposely allow passage of heparin and other relatively large solutes *See e.g.*, Shettigar, col. 7, lns. 33-44. Shettigar's filter has pores sizes up to 1.0mu (1 micron = $1* 10^{-6}$ m) which allows molecules significantly greater than 5 million Daltons in size to pass through. Shettigar's filter pore sizes are 1 micron which is about 500 times greater than an ultrafiltrate filter pore size. Shettigar teaches away from a small pore filters used for ultrafiltration. *See e.g.*, Shettigar, col.1, lns. 28-47.

Shettigar does not suggest that its filter having a small area and low flow is suitable for removal of filtrate. Shettigar does not suggest the claimed ultrafiltration system having a filter membrane that blocks heparin and other solutes in blood having a size greater than 60,000 Daltons. Shettigar specifically teaches transporting plasma across

a filter membrane in a blood circulation system into a plasma chamber containing an electrolyte plasma chamber solution followed by the selective removal of plasma components using sorbents, and to immobilized enzymes or antibodies in the plasma and does not disclose the design of a smaller pore fiber for the removal of ultrafiltrate. If a plasma removal filter were used for fluid removal important proteins and albumin would be removed from the patients blood stream placing the patient at grave physical risk. Accordingly, Shettigar teaches away from filtrate removal.

The design constraints for a plasma filter and an ultrafiltrate filter are different. Shettigar col. 7, lns. 45-49 (emphasis supplied), teaches as a design constraint that "the hollow fiber filter dimensions (hollow fiber lumen diameter, length of each hollow fiber and the number of fibers) and the blood flow rate through the fiber have to be optimized based on the art of membrane ***plasma*** separation and enzyme engineering". The design constraint imposed on Shettigar's plasma separation filter is distinct from that of a membrane for ultrafiltration. Shettigar's filter is designed to avoid "damage to the blood cells" which "may occur if the transmembrane pressure is increased beyond a particular limit" or "high shear rate." Fouling is not an issue in the Shettigar filter because the protein materials that can cause fouling pass easily through the large pores in the fiber walls.

In contrast to the problems faced by Shettigar's plasma separation filter, the small pore filters of the claimed invention face fouling and clotting. See, spec. p. 28, lns. 4-8. To avoid fouling and clotting in the filter, the shear rate of the blood flow is kept high.

The high shear rate results from a high blood flow rate through the filter and a low filter surface area. Claim 63 recites a high shear rate for the filter. Due to the high shear rate, the pores in the filter membrane are protected from fouling by particles. The small filter surface area and high blood flow rate minimizes the initiation of clotting as the blood passes quickly through the filter. Claim 59 recites a short residence time of blood in the filter and blood circuit.

Fecondini (see e.g., col. 3, lns. 33-38) discloses a hemodiafiltration cartridge having a second membrane that removes waste from blood, and is formed by hollow fibers a molecular having weight pore size cut-off of no greater than 55,000 daltons and preferable a cut-off in a range of 30,000 to 50,000 daltons. Fecondini, col. 4, lns. 4-25; col. 3, lns. 35-37. Fecondini does not suggest that the active filter membrane surface be no greater than 0.2 m^2, as required by independent claims 55 and 64 of this application. Given that the filter disclosed in Fecondini is for a hemodiafiltration apparatus (see col. 1, lns. 55-60) which require large surface areas because it relies primarily on diffusion, it is most likely that the filter would have a filter surface much larger than 0.2m^2. See current specification at p. 18, ln. 16 to p. 21, ln. 21 ("filters used for CVVH in adult patients have the membrane surface area of 0.7 – 2m^2" at p. 20, lns. 11-12). There is no suggestion in Fecondini that a filter surface area of no greater than 0.2 m^2 is sufficient for performing ultrafiltration.

Shettigar provides no suggestion to reduce the Fecondini filter membrane surface area to 0.2m^2. There is no suggestion to combine the plasmafilter of Shettigar and the

hemodiafiltration device of Fecondini to form the ultrafiltration filter of the present invention. Shettigar teaches away from ultrafiltration by disclosing a blood purification filter. *See* Shettigar, col. 1, lns. 28-34. To reduce the filter to the small diameter pores of the Fecondini filter would render the Shettigar filter incapable of performing purification. It would not have been obvious to modify the Fecondini filter *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994)(" A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.").

With respect to specific claims:

- Independent claims 55 and 64 require filtrate removal from a filter and that the filter membrane surface by less than 0.2 m^2, which is not disclosed in Shettigar or Fecondini. Claim 65 limits the surface to 0.1 m^2.
- Claim 55 requires the amount of the removed filtrate to be an effective therapeutic amount for treating a fluid overload condition of the patient, which is not disclosed in Shettigar.
- Claim 56 requires concentration of the blood, which is not suggested by Shettigar.

- Claims 57 requires the filtrate rate to be less than one liter per hour, claim 58 requires the blood flow through the filter to be in a range of 10 to 60 milliliters per minute, and claim 59 limits the blood residence time to no more than two minutes, which limitations are not suggested by Shettigar or Fecondini.
- Claims 62 and 71 limit the filter diameter to no more than 1.5 cm, which feature is not disclosed in Fecondini or Shettigar.
- Claims 62 and 70 require the filter to be substantially straight. The U-shaped filter disclosed in Shettigar creates reverse filtration at the exit of the filter. The U-shaped filter causes circulation within the plasma section of the housing facilitating the absorption of contaminants from the plasma. The straight filter recited in claims 62 and 70 is contrary to the Shettigar filter.
- Claim 66 limits the volume of the blood passage in the filter to less than two percent of a cardiac output of an adult, which feature is not suggested in Shettigar or Fecondini.

All claims are in good condition for allowance. If any small matter remains outstanding, the Examiner is requested to telephone the undersigned. Prompt reconsideration and allowance of this application is requested.

Respectfully submitted,

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